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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,791	11/10/2003	Kenneth Chien	041673-1202	5197

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,791	CHIEN ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,23,24,32,34 and 35* is/are pending in the application.

4a) Of the above claim(s) *25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,23,24,32,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment received on 03/02/05 has been entered.

Claims 18, 23, 34 have been amended. New claim 35 has been added. Claims 25-31 are withdrawn from further consideration as being drawn to a nonelected invention.

Claims 18-19, 23-24, 32, 34-35 are pending.

Oath/Declaration

2. It is noted that the Oath/Declaration has not been amended as have been requested in previous Office Action. Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Priority

3. Amendment to Priority has been entered. It is noted that this application appears to claim subject matter disclosed in prior divisional application of U.S. Patent Application Serial No. 09/705,791, filed on November 10, 2003, still pending, which in turn claims the benefit of priority of U.S. Provisional Application Serial No, 60/106,718, filed on November 2, 1998; International Application No, PCY/US99/25692, filed November 2, 1999; and U.S. Provisional Application, 60/145,883, filed July 27, 1999.

Claim Objections

4. Claim 23, is objected to because of the following informalities: Claim recites the phrase "wherein the the mutation" is grammatically incorrect. Appropriate correction is required.

Response to Arguments

5. Applicant's arguments filed 3/2/06 have been fully considered but they are not persuasive. It is noted that the enablement rejection has been changed compared to the previous office action and therefore, applicant's arguments would be addressed to the extent they read on the instant grounds of rejection.

In page 7, applicants argue that as to the viability of methods for gene therapy of human disease in general, Applicants submit that they have no obligation to address the prospects for clinical success in gene therapy in any condition other than, which they claim to treat. Moreover, Applicant need not to prove the efficacy of even the claimed methods, but only that they have enabled their use to an extent sufficient to meet the requisites of 35 U.S.C. & 112, first paragraph as the Federal Circuit advises In re Brana, 34 U.S.P.Q.2d 1436, 1442-1443 (Fed. Cir. 1995). In response, it is agreed that Applicants do not have to teach treatment for any condition other than, which they claim to teach but Applicants have to demonstrate that the recombinant mutant protein is produced and the gene therapy methods cannot be generalized and a method that is applicable to one disease would not be applicable to other disease(s) and the results in vitro can not always be extrapolated to the treatment of a disease in vivo as discussed above by experts in the art at the time of the invention or even after the filing of the instant application. In response, it is agreed that Applicants do not have to teach treatment, but Applicants have to demonstrate that the recombinant protein is produced by way of the claimed methods. The gene therapy methods cannot be generalized and a method that is applicable to one disease would not be applicable to other diseases and that results in experimental animals cannot always be extrapolated to humans. It is emphasized that the importance of gene therapy is not contested but rather what is contested is that the gene therapy method is not routine and one method cannot be applied to every disease or condition.

In page 8, 1st paragraph, Applicants argue that the assertion that gene therapy is an unpredictable art because the transfection efficiency and duration of expression achievable with a given construct can vary is not compelling. Applicants argue that that expression in cardiac myocytes achievable using the methods of the invention, whether transient or longer, should suffice to produce a therapeutic benefit and direct the Examiner to the Giordano et al, reference wherein intracoronary gene transfer of fibroblast growth factor-5 increases blood flow and contractile function in an ischemic region of the heart. In page 8, 2nd paragraph, Applicants argue that it is well known in the art that one advantage offered by certain viral vectors is the relative high transfection efficiency they can achieve and direct the Examiner to Verma and Weitzman reference and to the Sakoda et al reference. Applicants argue that those of ordinary skill in the art would recognize the suitability of the viral vectors presently taught for use in the methods of the invention and be able to construct them without undue experimentation. In response, this is not found persuasive because as discussed above by the experts in the field the transfection efficiency and duration of expression achievable with different constructs varies and Applicants have not shown that either transient or persistent expression of the said mutant(s) PLB product at sufficient levels in vivo in cardiac myocytes to treat said conditions by way of the claimed methods.

Therefore, it is maintained that lack of guidance and working examples pertaining to PLB gene therapy for treating conditions associated with the loss of cardiac muscle contractility or congestive heart failure by way of the claimed methods, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18 and 23, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The specification as filed does not teach a dominant negative phospholaban molecule wherein the expression of the dominant negative phospholaban product abrogates the normal function of the native phospholaban protein and wherein such abrogation correlates to the treatment of a condition associated with loss of cardiac muscle contractility. There is no evidence in the specification contemplating the use of a phospholaban dominant negative molecule as embraced by claims 18 and 23 and as claims 18 and 23 have been amended. Therefore, this is a new matter, not presented in the specification originally filed and therefore it cannot be used for supporting enablement of the instantly claimed invention.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 19, 24, 32, 34-35, are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

It is noted that, claims 32 and 34 limit the mutated phospholaban to specific point mutations consisting of R14E, S16N, S16E or K3E/R14Eor V49A. The specification as filed does not teach any dominant negative mutated phospholaban molecule including the instantly claimed mutated phospholaban molecules. In addition, the specification does not provide any guidance and/or working examples, which correlate the expression of such dominant negative molecules to the abrogation of the native molecule resulting in the treatment of a condition associated with loss of cardiac muscle contractility.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

8. Claims 18-19, 23-24, 32, 34-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention encompasses a method of treating conditions associated with the loss of cardiac muscle contractility comprising delivering an expression construct encoding a phospholamban (PLB) molecule having single or double point mutations in Domain I or II thereof, wherein the mutation is sufficient to provide the PLB molecule with dominant negative characteristics to accelerate sarcoplasmic reticulum calcium uptake (SERCA2a) mediated calcium transport in the myocytes to improve cardiac muscle contractility. Embodiments limit the construct to a viral vector. Embodiments also limit the mutation to a point mutation consisting of R14E, S16N, S16E or K3E/R14E or a V49A. Further embodiments limit the condition to be treated to congestive heart failure.

The specification teaches that using recombinant adenoviruses cardiac murine myocytes, which overexpress V49A, one of the single point mutations of PLB, exhibit an increase in contractility (length change in myocytes), compared to control myocytes, in vitro (specification p 17 and figure 5). The specification also teaches that neonatal rat myocytes infected with recombinant adenovirus carrying the transgene K3E/R14 show a decrease in the concentration of Ca^{2+} needed by SERCA2a for the same activity compared to control myocytes indicating a stimulation of SERCA2a activity while in adult rat myocytes the effect is not within statistical significance indicating the unpredictability of the effect of the mutant PLB on SERCA2 activity among different animal species (specification p 19). The specification also mentions the in vivo cardiac gene transfer by injecting the adenovirus vectors carrying the transgene V49A into 1 day old neonatal mouse heart, expression of the transgene was detected in 4 day-old isolated myocytes, in vitro (specification p 28). While the specification contemplates treatment of heart failure by inhibiting the interaction between PLB and SERCA2a in cardiac tissue by way of the claimed methods (specification p 6), however, the specification has failed to provide any guidance and/or working examples that correlate to the treatment of a condition associated with

cardiac muscle contractility or congestive heart failure by way of the claimed methods. It appears that the guidance provided by the instant specification fails to correlate to the production of a therapeutic protein in vivo resulting in the treatment of a condition associated with cardiac muscle contractility or congestive heart failure. As enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating claimed diseases. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

Move ↓ response to arguments on pages 3-4

The claims are directed to a method of treating a disease in a subject by expressing PLB mutants in cardiac myocytes wherein the mutation is sufficient to provide the PLB molecule with dominant negative characteristics and further expression of the polynucleotide accelerates SERCA2 mediated calcium ion transport in the treated myocytes to improve cardiac muscle contractility. Since the specification has failed to provide specific guidance and/or working examples correlating to the treatment of a cardiac condition associated with loss of cardiac muscle contractility such as congestive heart failure by way of the claimed methods, one of skill in the art could not rely on the state of the gene therapy art to treat any of the claimed cardiac conditions by way of the claimed methods. This is because the art of gene therapy is an unpredictable art with respect to cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. Numerous factors complicate the gene delivery cell targeting. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction taken up by the target population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, and the protein's

compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the various viral vectors used and the protein being produced. In the instant case, it is claimed the use of any viral vector for practicing claimed method. While progress has been made in recent years for gene transfer, vector targeting to desired organs continuous to be unpredictable and inefficient. This is supported by numerous teachings in the art. **Thomas et al,** (Nature, 4: 346-358, 2003) while reviewing the status of art with respect to the progress and problems with the use of viral vectors for gene therapy reports that adenovirus vectors are the most immunogenic of all the viral vector groups, and the largest hurdle that has faced gene therapists using adenovirus vectors is overcoming immunogenicity (p 352, 2nd column). Induction of humoral as well as cellular immune response against viral capsid itself or viral gene products or against the transgene still pose an issue of adenovirus vector use as vehicle for gene transfer (p 352, 2nd column). **Thomas et al,** went onto say other vector systems are less immunogenic such as AAV and lentivirus vectors but, T-cell responses can still be elicited against the expressed transgene product, and route of administration has profound effect on the development of T-cell responses to transgene that are expressed from AAV vectors (p 353, 2nd column). As more work is needed to develop site-specific integrating vectors, more work is also needed to improve the ability of vectors to home in on and infect specific target-cell populations and understanding how to predict the response of individual patients to inflammatory vectors also remains a substantial challenge (p 356, 1st column). **Thomas et al,** concludes that there is still a tremendous amount of work to be done in gene therapy on improving vectors (p 356, 2nd column). **Gardlik et al,** (Med Sci Monit, 111(4): RA110-121, 2005) while reviewing the state of the art of vector delivery systems in gene therapy concludes that a number of methods have been invented for the delivery of therapeutic DNA, however, there is no clear ideal delivery system and the perspectives and hopes that are

associated with gene therapy support research in the field of molecular biomedicine (p RA119). **Zaiss et al,** (Curr Gene Therapy, 5: 323-331, 2005) also notes that one of the biggest challenges in optimizing viral vectors for gene therapy relates to the immune response of the host (abstract). **Zaiss et al,** notes that AAV-mediated gene therapy leads to development of antibodies against the vector capsid and anti-AAV antibodies have neutralizing effects that decrease the efficiency of in vivo gene therapy and AAV vectors can induce cellular and host immune response against the transgene product (abstract). Both cellular and humoral responses to the delivered gene depend on a number of variables; including the nature of the transgene, the promoter used, the route and site of the administration vector site and host factors (**Zaiss et al,** abstract).

The most pressing issue that the field of gene therapy has to address is the development of efficient in vivo gene delivery systems. In the instant case, the specification does not provide guidance as to how any viral vector encoding for any of the claimed mutant PLB molecule(s) will be directed to cardiac myocytes and whether sufficient amount of mutant PLB molecule(s) could be produced to result in the treatment of a cardiac condition by way of the claimed methods. The specification does not provide any guidance as to what doses or mode(s) of administration of a viral vector carrying said mutant PLB will be sufficient to target a viral vector to cardiac myocytes. At the time of the instant invention, the art teaches that adenoviral vectors carrying cDNA for either wild type PLB or beta-galactosidase or modified green fluorescence protein (EGFP) two days after infection via catheter based technique, rat hearts transduced with Ad.PLB had lower peak left ventricular pressure compared with uninfected or Ad.beta-galactosidase (**Hajjar et al,** Proc Natl Acad Sci, 95: 5251-5256, April 1998) (p 5251 abstract). However, the authors further note: "Eventhough our delivery method was specifically targeted to the heart we found expression of the reporter transgene in other

tissues in the body, such as lung liver but not in aorta. **Schroder et al,** (Expert Opin Biol Ther, 4(9): 1413-1422, 2004) while reviewing vectors used for cardiac gene delivery, even after the filing of the instant application, notes that, although viral vectors appear to have significant utility for application in the cardiovascular system, at the present time, no single vector system appears ideal (p 1414, 1st column). **Schroder et al,** also reviewed the status of gene therapy for altered Ca^{2+} handling in heart failure including the applicant's use of rAAV vector carrying a dominant negative mutant of PLB which suppressed development of heart failure to cardiomyopathic hamsters concludes that although research has demonstrated effects on animal models of heart failure, questions of optimal gene delivery and attempts to identify vectors that yield reproducibly efficient gene transfer in cardiac myocytes with limited effects on non-target organs is needed (p 1419).

In light of the above, it appears that the state of the art is suggesting that said mutant(s) PLB gene therapy is unpredictable and lack of evidence of a method of treating any condition associated with loss of cardiac muscle contractility or congestive heart failure with said mutant PLB gene. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of said mutant PLB gene therapy raised by the art. Therefore, the skilled artisan would conclude that the state of the art of said mutant PLB gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided the instant specification, it would have required undue experimentation to practice the invention as claimed for treating conditions associated with loss of cardiac muscle contractility or congestive heart failure by said mutant PLB gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a condition associated with loss of cardiac muscle

contractility or congestive heart failure, the lack of direction or guidance provided by he specification for treatment of said condition, the absence of working examples that correlate to the treatment of said condition, the unpredictable state of the art with respect to gene therapy, and in particular mutant PLB gene transfer in vivo to cardiac myocytes of the heart, the undeveloped state of the art pertaining to the treatment of said conditions, and the breadth of the claims directed to any condition associated with loss of cardiac muscle contractility or congestive heart failure, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the limitation "the inhibitory activity" in line 2-3. There is insufficient antecedent basis for this limitation in the claim. It is not clear what is meant by inhibitory activity because claim 18 recites a mutation sufficient to provide the PLB molecule with dominant-negative characteristics.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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